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FORM PTO-1390 (REV. 11-94) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: 3006-0044

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

10/088004 PCT

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB00/01280	September 8, 2000	September 9, 1999

TITLE OF INVENTION
USE OF CONJUGATED LINOLEIC ACID (CLA) FOR THE TOPICAL TREATMENT OF CELLULITE

APPLICANT(S) FOR DO/EO/US
Carlo GHISALBERTI

Applicant herewith submits to the United States Designated/ Elected Office (DO/EO/US) the following items under 35 U.S.C. 371:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the international Bureau)
   b ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☒ Amendments to the claims of the International Application under PCT Article 34
   a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureaus.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 37(c)(3)).

9. ☒ An unexecuted oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☐ Other items or information:

Copies of. International Publication No. WO01/17498 A1; International Preliminary Examination Report (PCT/IPEA/409); PCT International Search Report (PCT/ISA/210).

INTERNATIONAL APPLICATION NO PCT/IB00/01280 10/088004	INTERNATIONAL FILING DATE September 8, 2000	JC13 Rec'd PCT/PTO 11 MAR 2002

17. ☒ The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees as follows:

CLAIMS				
(1)FOR	(2)NUMBER FILED	(3)NUMBER EXTRA	(4)RATE	(5)CALCULATIONS
TOTAL CLAIMS	19 -20	0	X $18.00	$ 0.00
INDEPENDENT CLAIMS	3 -3	0	X $84.00	0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $280.00	☐
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): **CHECK ONE BOX ONLY** ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) $710.00				
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $740.00				
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,040.00				
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2) to (4) $100.00				
☒ Filing with EPO or JPO search report $890.00				$ 890.00
Surcharge of $130.00 for furnishing the National fee or oath or declaration later than 20 30 mos. from the earliest claimed priority date (37 CFR 1.492(e)).				$ 130.00
		TOTAL OF ABOVE CALCULATIONS		= 1,020.00
Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (Note 37 CFR 1.9, 1.27, 1.28).				- $ 510.00
		SUBTOTAL		= 510.00
Processing fee of $130.00 for furnishing the English Translation later than 20 30 mos. from the earliest claimed priority date (37 CFR 1.492(f)).				+
0		TOTAL FEES ENCLOSED		$ 510.00

a. ☐ A check in the amount of $__ to cover the above fees is enclosed.

b. ☒ Please charge Deposit Account No. 16-1150 in the amount of $ 510.00 to cover the above fees. A copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 16-1150. A copy of this sheet is enclosed.

18. ☐ Other instructions

n/a

19. ☒ All correspondence for this application should be mailed to

PENNIE & EDMONDS LLP
1155 Avenue of Americas
New York, N.Y. 10036-2711

20. ☒ All telephone inquiries should be made to

Charles E. Miller		24,576	March 11, 2002
NAME	SIGNATURE	REGISTRATION NUMBER	DATE

Express Mail No.: EL 477 035 174 US
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Carlo GHISALBERTI

Group Art Unit: To be assigned.

Serial No.: To be assigned.

Examiner: To be assigned.

Filed: March 11, 2002

Attorney Docket No.: 3006-0044

For: USE OF CONJUGATED LINOLEIC ACID (CLA) FOR THE TOPICAL TREATMENT OF CELLULITE

New York, New York
March 11, 2002

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to the examination of the above-identified application, please enter the following amendments and remarks into the file of the subject application.

IN THE CLAIMS:

Please cancel claims 1-10.

Please add the following new claims:

11. A cosmetic or dermatological topical composition comprising a conjugated linoleic acid or a derivative thereof (CLA).

12. The topical composition according to claim 11 comprising from 0.5 to 70% by weight of CLA.

13. The topical composition according to claim 12, wherein the CLA comprises a member selected from the group consisting of cis- and trans- isomers of 9,11-; 10,12-; and 11,13-octadecadienoic acid, and phospholipid, mono-, di- and tri-glycerides, ethers, esters, and salts thereof.

14. The topical composition according to claim 13, wherein the salt of CLA is an alkali or alkaline earth metal soap, or a nitrogen-containing salt.

15. The topical composition according to claim 11 which is in the form of cream, gel, lotion, oil or spray.

16. The topical composition according to claim 11 further comprising one or more anti-cellulite agents.

17. The topical composition according to claim 16, wherein the anti-cellulite agent is a xanthine.

18. The topical composition according to claim 17, wherein the anti-cellulite agent is selected from the group consisting of caffeine, theophulline, theobromine, aminophylline and mixture thereof.

19. The topical composition according to claim 11 further comprising a vanadium compound.

20. A method of treating or preventing fatty deposits and cellulite comprising topically administering a conjugated linoleic acid or a derivative thereof (CLA).

21. A method of treating or preventing fatty deposits and cellulite comprising topically administering a cosmetic or dermatological composition comprising a conjugated linoleic acid or a derivative thereof (CLA).

22. The method according to claim 21, wherein the composition comprises from 0.5 to 70% by weight of CLA.

23. The method according to claim 22, wherein the CLA comprises a member selected from the group consisting of cis- and trans- isomers of 9,11-; 10,12-; and 11,13-octadecadienoic acid, and phospholipid, mono-, di- and tri-glycerides, ethers, esters, and salts thereof.

24. The method according to claim 23, wherein the salt of CLA is an alkali or alkaline earth metal soap, or a nitrogen-containing salt.

25. The method according to claim 21, wherein the composition is in the form of cream, gel, lotion, oil or spray.

26. The method according to claim 21, wherein the composition further comprises one or more anti-cellulite agents.

27. The method according to claim 26, wherein the anti-cellulite agent is a xanthine.

28. The method according to claim 27, wherein the anti-cellulite agent is selected from the group consisting of caffeine, theophulline, theobromine, aminophylline and mixture thereof.

29. The method according to claim 21 further comprises a vanadium compound.

REMARKS

Claims 1-10 are herein canceled and replaced with new claims 11-29. The new claims correspond to the subject matter of the canceled claims but are presented in the form which conforms with the current practice under the United States Patent Law. No new matter is added.

No fee is believed to be due for this amendment. Should any fee be required, please charge it and any other fee that may be required or appropriate in connection with this submission to Deposit Account No. 16-1150. A copy of this page is enclosed.

Respectfully submitted,

Date March 11, 2002

24,576

Charles E. Miller (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Attorneys For Applicant

Attachment: Exhibit A

EXHIBIT A

PENDING CLAIMS

UPON ENTRY OF THE PRESENT PRELIMINARY AMENDMENT

(Filed March 11, 2002)

Attorney Docket No. 3006-0044

Please cancel claims 1-10.

Please add the following new claims:

11. A cosmetic or dermatological topical composition comprising a conjugated linoleic acid or a derivative thereof (CLA).

12. The topical composition according to claim 11 comprising from 0.5 to 70% by weight of CLA.

13. The topical composition according to claim 12, wherein the CLA comprises a member selected from the group consisting of cis- and trans- isomers of 9,11-; 10,12-; and 11,13-octadecadienoic acid, and phospholipid, mono-, di- and tri-glycerides, ethers, esters, and salts thereof.

14. The topical composition according to claim 13, wherein the salt of CLA is an alkali or alkaline earth metal soap, or a nitrogen-containing salt.

15. The topical composition according to claim 11 which is in the form of cream, gel, lotion, oil or spray.

16. The topical composition according to claim 11 further comprising one or more anti-cellulite agents.

17. The topical composition according to claim 16, wherein the anti-cellulite agent is a xanthine.

18. The topical composition according to claim 17, wherein the anti-cellulite agent is selected from the group consisting of caffeine, theophulline, theobromine, aminophylline and mixture thereof.

19. The topical composition according to claim 11 further comprising a vanadium compound.

20. A method of treating or preventing fatty deposits and cellulite comprising topically administering a conjugated linoleic acid or a derivative thereof (CLA).

21. A method of treating or preventing fatty deposits and cellulite comprising topically administering a cosmetic or dermatological composition comprising a conjugated linoleic acid or a derivative thereof (CLA).

22. The method according to claim 21, wherein the composition comprises from 0.5 to 70% by weight of CLA.

23. The method according to claim 22, wherein the CLA comprises a member selected from the group consisting of cis- and trans- isomers of 9,11-; 10,12-; and 11,13-octadecadienoic acid, and phospholipid, mono-, di- and tri-glycerides, ethers, esters, and salts thereof.

24. The method according to claim 23, wherein the salt of CLA is an alkali or alkaline earth metal soap, or a nitrogen-containing salt.

25. The method according to claim 21, wherein the composition is in the form of cream, gel, lotion, oil or spray.

26. The method according to claim 21, wherein the composition further comprises one or more anti-cellulite agents.

27. The method according to claim 26, wherein the anti-cellulite agent is a xanthine.

28. The method according to claim 27, wherein the anti-cellulite agent is selected from the group consisting of caffeine, theophulline, theobromine, aminophylline and mixture thereof.

29. The method according to claim 21 further comprises a vanadium compound.

USE OF CONJUGATED LINOLEIC ACID (CLA) FOR THE TOPICAL TREATMENT OF CELLULITE

FIELD OF THE INVENTION

The present invention relates to the use of conjugated linoleic acid (CLA) for the topical treatment of fatty deposits and cellulite and to new topical compositions.

More particularly, the invention relates to cosmetic and dermatological topical compositions for the cosmetic treatment of fatty deposits and cellulite comprising CLA as well as kits comprising CLA for said treatment.

BACKGROUND OF THE INVENTION

Conjugated linoleic acid (CLA) is a mixture of positional and configurational isomers of octadecadienoic acid, which are naturally occurring substances found in milk and diary products as well as in meats of ruminants.

The term CLA includes the family of positional and configurational isomers of C18:2 fatty acid, more precisely the cis and trans form of 9,11-10,12- and 11,13-octadecadienoic acids.

Many studies reported that synthetic CLA is an effective agent in inhibiting mammary, colon, forestomach, and skin carcinogenesis in experimental models, due to its modulation of lymphocyte and macrophage activities. Recent clinical and in vivo data disclosed novel biological effects of CLA, e.g. the anti-atherogenic and anti-hyperinsulinemic activities.

After having attracted the attention of the international scientific

community for its therapeutic properties above, CLA is gaining further consumer acceptance as nutritional supplement as it has been shown that a CLA-enriched diet produces a significant improvement in overall health conditions.

CLA is also known as a slimming agent, whose oral consumption produces a marked decrease of body fat with increase in the lean body mass. The effects of CLA on body fat/lean ratio seem to be due to inhibition of both proliferation and differentiation of preadipocytes, as observed by Brodie A.E. et al. in J. Nutr. 129:602-6 (1999).

The use of CLA in topical composition and cosmetic method for treating skin conditions selected from the group consisting of wrinkling, sagging, photodamaged skin, sensitive skin, dry skin, flaky skin, red skin, irritated skin, itchy skin and age spots, is disclosed in WO0037040.

Topical compositions of zinc salts of CLA for the treatment of skin disorders, such as eczema, psoriasis and dermatitis and so on WO98/17269 discloses. However, the use of zinc salts of CLA is limited to pharmaceutical and dermatological purposes only. Moreover, the poor solubility of the zinc salts of CLA, either in lipophilic and hydrophilic media, significantly decreases the bioavailability of the active ingredient in said topical treatment.

DETAILED DESCRIPTION OF THE INVENTION

It is appreciated that in the present specification the term CLA is intended to include either CLA in the form of free fatty acid or its derivatives, such as its phospholipid, its mono-, di- and tri-glycerides, ethers, esters or salts thereof. All derivatives must be physiologically acceptable, i.e. non-toxic derivatives of CLA. Preferred salts of CLA include the metallic soaps of CLA

with alkaline and/or earth-alkaline ions, such as sodium, potassium, or magnesium ions, and the nitrogen-containing salts, such as ammonia, mono-, di- or tri-ethanolamine.

We have first envisaged the possibility to use CLA in the treatment of cellulite, the skin dimpling of the thighs and buttocks caused by dermohypodermosis and oedemato-sclerous panniculopathy, in which the fibroblastic reaction predominates over capillaro-veinular changes.

As observed by Rosenbaum M; Prieto V; Hellmer J; Boschmann M; Krueger J; Leibel RL; Ship AG (Plast Reconstr Surg, 101(7):1934-9 1998), in vitro pathologic examination of wedge biopsies and in vivo sonographic examination of the thigh both showed a diffuse pattern of extrusion of underlying adipose tissue into the reticular dermis.

Adipocytes of exaggerated size interpenetrate into micronodules and later into macronodules marked off by more or less structured conjunctive fibrilla, as quoted by Merlen JF; Curri SB; Sarteel AM (Phlebologie, 32(3):279-82, 1979).

Due the uncertainty of cellulite aetiology, said unaesthetic condition has been so far treated with a variety of active ingredients, each acting by different mechanisms.

We have now found out that the topical administration of CLA accelerates and provokes the reduction of fatty deposits.

We have consequently found out that CLA is effective in the topical treatment of the impaired aesthetic conditions caused by subcutaneous fat deposition, particularly on pannicular adiposis, said topical treatment leading to a significant improvement of the cellulite conditions.

Therefore, one of the objects of the present invention is the use of CLA for the topical treatment and/or prevention of fatty deposits and cellulite.

CLA is particularly suitable for the topical anticellulite treatment; it is a natural product which showed no observed adverse effects or toxicity in humans after topical treatment. After several applications on people of both sexes having derma either in normal or in pathological status, e.g. erythema and itching derma, no phenomena showing intolerance to the product occurred.

The physical and chemical properties of CLA are particularly appropriate for a topical skin treatment, as it displays good lipid solubility and is easily absorbed onto the horny layer.

According to another of its aspects, the present invention concerns a cosmetic and dermatological topical composition, useful for treating and/or preventing cellulite and fatty deposits.

According to a further aspect, the invention concerns a method for the treatment of cellulite which comprises topically administering to a subject an effective amount of CLA, either alone or in the form of a topical composition.

In order to exploit the cosmetic treatment of the invention CLA is preferably administered in the form of a topical composition, said composition having a content of CLA of from 0.5 to 70% by weight, preferably from 1 to 30% by weight, more preferably from 2 to 5% by weight, optionally in admixture with suitable customary auxiliary agents.

In a preferred embodiment of the present invention, CLA is combined with one or more well-known anti-cellulite agent.

Particularly preferred common common anti-cellulite agents are substances showing beta-stimulation (adrenergic beta-agonists) to further enhance lipolysis into the dermal adipocytes. Examples of such substances are xanthines such as caffeine, theophylline, theobromine and aminophylline, which are characterized by a high skin availability and an high efficacy. Xanthines are preferably employed in an proportion of at least 0.05%, generally in an proportion of from 0.05% to 20%, preferably from 0.10% to 10%, optimally from 0.5% to 3.0% by weight of the composition in order to maximize efficacy at optimum cost.

Other preferred common anti-cellulite agents are substances acting as collagen synthesis stimulators, such as ascorbates and triterpenoids of Centella asiatica, e.g. asiatic acid, madecassic acid, asiaticoside, madecaside, inositol phosphate, and phytic acid.

Other preferred common anti-cellulite agent are substances which improve the poor vascularity condition associated to the cellulitic areas by a vasokinetic activity, such as minoxidil, nicotinates, escin, ivy, and methyl salicylate.

Other preferred common anti-cellulite agent are natural substance exerting adenylate cyclase agonist and/or anti-phosphodiesterase activities, which accelerate the reduction of fatty deposits located in the cellulite affected area. The former group may include extracts from Ipomea spp., from Salvia spp. and from Rosmarinus officinalis, the latter group the yohimbine-type alkaloids and those plant extracts (e.g. ginkgo biloba) which contain dimeric flanones such as amentoflavone, bilobetine, sciadopitisine, ginkgonetine, or extracts from some Malvaceae (e.g. Malva, Althea,

Hibiscus, Hoheria, Sidalcea, Abutilon and Gossypium).

For the treatment of cellulite and fatty deposits, topical CLA may also be used in combination with vanadium compounds.

Vanadium compounds are known to act as insulin-mimetic substances, thus as being capable to enhance glycolisis and metabolic turn-over in cells, including adipocytes.

Therefore, according to a particular embodiment, the present invention relates to a cosmetic composition comprising CLA and at least a vanadium compound.

Vanadium (IV) or (V) compounds are suitably present at concentration in the range of 10^{-10} to 10^{-3} moles/kg, preferably 10^{-7} to 10^{-5} moles/kg in the cosmetic compositions of the present invention.

Illustrative examples of suitable vanadium (V) compounds useful in the practice of the present invention include sodium metavanadate ($NaVO_3$), orthovanadate (Na_3VO_4) and pyrovanadate ($Na_4V_2O_7$), corresponding salts with potassium (KVO_4), ammonium (NH_4VO_3), calcium ($Ca_3(VO_4)_2$), iron ($Fe(VO_3)_3$), and corresponding salts of vanadates with magnesium, zinc, aluminum, and the like; the vanadium (V) oxides such as the pentoxide (V_2O_5), oxytrichloride ($VOCl_3$), oxytribromide ($VOBr_3$) and the like, as well as polymers such as a dimer ($H_2V_2O_7$), a trimer (V_3O_9), a decamer ($HV_{10}O_{28}$), and the like.

Illustrative examples of suitable vanadium (IV) compounds useful in the practice of the present invention include vanadyl sulfate ($VOSO_4$), and corresponding compounds with acetate, etc; vanadium (IV) oxyhalides such as the oxychloride ($VOCl_2$), oxydibromide ($VOBr_2$), and oxydifluoride (VOF_2);

vanadium (IV) halides such as the tetrachloride (VCl_4), tetrabromide (VBr_4) and tetrafluoride (VF_4) and the like; vanadium dioxide (VO_2) and vanadium tetraoxide (V_2O_4).

Furthermore, the vanadium (IV) or (V) compounds may be present in form of chelates, clathrates or other complexes, including those with amino acids, proteins, peptidic growth factors, nucleic acids, phosphates, phospholipids, fatty acids, prostaglandins, AHAs, retinoids, tris-edatate, glycols, catechols, glutathione, and the like.

The vanadium (IV) or (V) compounds may also be present as salts of organic acids and vanadium contained in tunicates (sea squirts), some mushroom species and plants, and other organic sources. Specific examples of vanadium organometallic compounds include vanadyl salts of organic acids such as: vanadyl linoleate, oleate, palmitate, phenolate, resinate and stearate.

All the compositions according to the invention may also comprise any cosmetically acceptable ingredients. The expression "cosmetically acceptable ingredients" designate in the present specification products which are suitable for their use in cosmetic treatments, for example those included in the INCI list drawn by the European Cosmetic Toiletry and Perfumery Association (COLIPA) and issued in 96/335/EC "Annex to Commission Decision of 8 May 1996".

A variety of active ingredients may further be added to the compositions according to the present invention. Although not limited to this category, general examples include anti-inflammatory agents and skin whitening agents, antioxidants and anti-wrinkling agents.

Suitable anti-inflammatory compounds include, but are not limited to, rosmarinic acid, glycyrrizinate derivatives, alpha bisabolol, azulene and derivatives thereof, asiaticoside, sericoside, ruscogenin, escin, escolin, quercetin, rutin, betulinic acid and derivatives thereof, catechin and derivatives thereof.

Suitable skin whitening compounds include, but are not limited to, ferulic acid, hydroquinone, arbutine, and kojic acid.

Suitable antioxidants and anti-wrinkling compounds include, but are not limited to, retinol and derivatives, tocopherol and derivatives, salicylates and their derivatives.

Another important agent which can be added in the cosmetic composition according to the invention is an alpha-hydroxy acid. Preferred alpha-hydroxy acids are monocarboxylic acids, improving skin penetration and efficacy of CLA and further common anticellulite agents, such as lactic acid, glycolic acid, mandelic acid and mixtures thereof. Preferably, the proportion of the alpha-hydroxy acid component in the cosmetic composition of the invention is from 1.5% to 15%, more preferably from 3.0% to 12.0% by weight of the composition.

Another important optional ingredient is chosen among essential fatty acids (EFAs), exerting an important role in skin defence against oxidative stress, by entering in the lipid biosynthesis of epidermis and providing lipids for the barrier formation of the epidermis. Preferred essential fatty acids are selected from the group consisting of linoleic acid, gamma-linolenic acid, homo-gamma-linolenic acid, columbinic acid, eicosa-(n-6,9, 13)-trienoic acid, arachidonic acid, gamma-linolenic acid, timnodonic acid, hexaenoic

acid and mixtures thereof.

The cosmetic compositions of the invention can further comprise substances acting as dilutant, dispersant or carrier for CLA which are added to the compositions according to well known techniques in any suitable proportion well known to the skilled in the art, for example ranging from about 30% to about 99.9%, preferably from about 50 to 99.5% by weight of the total composition.

An oil or oily material may be present with water together with an emulsifier (alias "surfactant") to provide either w/o or o/w emulsions, largely depending on the average hydrophilic-lipophilic balance (HLB) of the emulsifier. Surfactants can be incorporated in any suitable proportion well known to the skilled in the art, for example from about 0.5% to about 30%, preferably from about 1% to about 15% by weight.

Cationic, nonionic, anionic, or amphoteric surfactants, and combinations thereof may also be employed. Nonionic surfactants may include alkoxylated compounds based upon fatty alcohols, fatty acids and sorbitan, copolymers of polyoxypropylene-polyoxyethylene, and alkyl polyglycosides. Anionic-type surfactants may include fatty acid soaps, sodium lauryl sulphate, sodium lauryl ether sulphate, alkyl benzene sulphonate, mono and/or dialkyl phosphates and the like. Amphoteric surfactants include dialkylamine oxides, various types of betaines and natural phospholipids.

In a water-based cosmetic composition, a thickener agent may also be present in any suitable proportion well known to the skilled in the art, for example from 0.1 to 10% by weight, preferably from about 0.5% to 5% by

weight. Exemplary thickener agent are cross-linked polyacrylate materials (Carbopol®), and gums such as xanthan, carrageenan, gelatin, karaya, pectin and locust beans gum. Said water-based cosmetic composition can be protected with preservatives against the growth of microorganisms. Suitable preservatives include alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, propionate salts, methyl paraben, propyl paraben, imidazolidinyl urea, sodium dehydroxyacetate benzyl alcohol, and a variety of quaternary ammonium compounds. Preservatives are added any suitable proportion well known to the skilled in the art, for example in proportion ranging from about 0.2% to 1% by weight.

In a fluid non-aqueous cosmetic composition, silicone polymers may also be present, in any suitable proportion well known to the skilled in the art, for example in amounts of ranging from 5 to 95% by weight.

Further ingredients that may be included in the cosmetic composition of the present invention are emollients. Under certain circumstances emollients may have dual functionality, acting both as carrier, to facilitate the dispersion of the CLA as active ingredient and skin softners. Emollients may be incorporated in the cosmetic composition of the invention in any suitable proportion well known to the skilled in the art, for example ranging from about 0.5% to about 50%. Suitable emollients may be classified under such general chemical categories as esters, fatty acids and alcohols, polyols and hydrocarbons. Appropriate fatty di-esters include dibutyl adipate, diethyl sebacate, diisopropyl dimerate, propylene glycol myristyl ether acetate, diisopropyl adipate, and dioctyl succinate. Appropriate branched chain fatty esters include 2-ethyl-hexyl myristate, isopropyl stearate and

isostearyl palmitate. Appropriate tribasic acid esters include triisopropyl trilinoleate, trilauryl citrate, tributirrine, and saturated or unsaturated vegetable oils. Appropriate straight chain fatty esters include lauryl palmitate, myristyl lactate, oleyl eurcate, stearyl oleate coco-caprylate/caprate, and cetyl octanoate. Appropriate fatty alcohols and acids are C_{10}-C_{20} compounds such as cetyl, myristyl, palmitic and stearyl alcohols and acids. Appropriate polyols are linear and branched chain alkyl polyhydroxyl compounds, such as propylene and butylene glycol, sorbitol glycerin, as well as polymeric polyols such as polypropylene glycol and polyethylene glycol. Appropriate hydrocarbons are linear C_{12}-C_{30} hydrocarbon chains such as mineral oil, petroleum jelly, squalene and isoparaffins.

Sunscreens may also be incorporated in the cosmetic composition of the invention. Illustrative compounds are the derivatives of PABA, cinnamate and benzophenone such as octyl methoxy-cinnamate, 2-hydroxy-4-methoxy-benzophenone. The proportion of sunscreens employed depends upon the degree of protection desired from the UV radiation.

Other minor components may also be added to the cosmetic composition of the invention, including colouring agents, opacifiers and perfumes each being optionally present in appropriate proportions for example from 0.001% up to 20% by weight of the composition.

The topical skin treatment composition of the invention can be formulated as a lotion, a fluid cream, a cream or a gel. The composition can be packaged in a suitable container according to its viscosity and to the intended use by the user. For example, a lotion or fluid cream can be

packaged in a bottle, in a roll-ball applicator, in a capsule, in a propellant-driven aerosol device or a container fitted with a pump suitable for finger operation. When the composition is a cream, it can simply be stored in a non-deformable bottle or in a squeeze container, such as a tube or a lidded jar.

According to another of its aspects the present invention relates to a kit for the topical administration of CLA.

Said kit comprises (a) unit dosage form compositions comprising CLA, optionally in admixture with suitable customary excipients and antioxidants, preferably in the form of an oily liquid and (b) unit dosage form comprising at least one hydrophilic anticellulite agent, optionally in admixture with suitable customary excipients and alpha-hydroxy acid, in aqueous or hydroalcoholic solution.

The kit packaging box further comprises an leaflet giving the instruction to apply first the aqueous solution (b) for the effective absorption of the hydrophilic ingredients, and secondly to apply the oily liquid (a).

One of the advantages of the kit is that the penetration of hydrophilic anticellulite agents is made easier in absence of the oily phase, which is subsequently applied to the skin.

The following examples show in detail how the present invention can be practiced but should not be intended as limiting it.

Preparative Example 1 - Synthesis of CLA by alcaline isomerization of grape seed oil in glycerol (The following synthesis makes the object of a co-pending application).

1 kg glycerol, 235 g potassium hydroxide (KOH) and 1000 g of grape seed oil were added into a 4-neck round bottom flask (5000 ml) equipped with a mechanical stirrer, a thermometer, a reflux condenser, and a nitrogen inlet, the nitrogen being introduced in first run through two oxygen traps.

Nitrogen was bubbled into the reaction mixture for 20 min and the temperature was then raised to 90-100 °C, and kept under mechanical stirring for about 20 minutes to convert the trigliceride in the corresponding potassium salts. The double phase system disappears to form a glyceric soap suspension, then heated at 230 °C under inert atmosphere and stirred for 4 hours.

The reaction mixture was cooled to about 100 °C, and the stirring stopped as the reaction mixture tend to reach very high viscosity during cooling. 2 l of water was then slowly added, and the mixture kept at 95°C for 2 hour. This operation becomes necessary because of the neglegible presence of water and high content of glycerol causing fatty acids to be present as mono- and diglyceride from 5% to 10% by weight of the total lipid content. As partial glyceride esters tend to form W/O emulsion, the water addition and re-heating provides full saponification of the residual esterified fatty acid.

The mixture was transferred into a becker, then cooled to room temperature and 50% w/v sulfuric acid was added to the mixture which was stirred for 1 hour until the pH stabilized at about 3.

The acidulated oil phase formed a lower hydroglyceric layer and an upper fatty acid oil layer containing CLA, which was separated by decantating. Noteworthy, in industrial operation the separation could be

carried out by centrifugation.

The CLA was washed with water and finally it was made anhydrous with sodium sulphate and filtered, then it is stored in a dark bottle at 4 °C until time of use. Total yield about 770 g af an amber oil, whose GC-analysis is shown in Table 1.

TABLE 1

Fatty Acid	Grape Seed (Starting material)	CLA from Grape Seed (Final Product)
C14:0	0.11	0.13
C16:0	6.53	6.56
C18:0	3.02	3.23
C20:0	0.19	0.20
total saturated	9.85	10.12
C16:1	0.42	0.48
C18:1	16.42	17.15
C18:1(t)	0.08	0.23
C20:1	0.59	0.60
total monounsaturated	17.51	18.46
C18:2	72.11	1.76
C18:2-conjugated (CLA)	0.21	69.48
C18:3	0.31	0.18
C20:3	0.01	0.00
total polyunsaturated	72.64	71.42

The composition of CLA appears to be a complex mixture, i.e. 9c,11t- and 8c,10t- octadecadienoic acids at 30,90 %, 11c,13t- 10t,12c- octadecadienoic acids at 32,05 %, 11t,13c- 8c,10c- 9c,11c- octadecadienoic acid at 1,55 %, 10c,12c- 11c,13c- 11t,13t , 9t,11t- 10t,12t- 8t,10t- octadecadienoic acids making the remaining part.

Comparative Example 1 and Applicative Examples 1, 2 – Body creams

Three different O/W emulsions were prepared under stirring by turbomixing the oily phase and the water phase, each separatedly preheated at 75° C; the compositions are shown herewithafter:

Ingredient	Emulsion of Comparative Example 1	Emulsion of Applicative Example 1	Emulsion of Applicative Example 2
Oily phase			
CLA from the Preparative Example 1	-	2.7 g	2.7 g
soybean fatty acids	2.7 g	-	-
poliglyceryl-2-sesquistearate	1.0 g	1.0 g	1.0 g
bees wax	0.3 g	0.3 g	0.3 g
magnesium stearate	0.5 g	0.5 g	0.5 g
aluminum stearate	0.5 g	0.5 g	0.5 g
hydrogenated castor oil 7-PEO	2.0 g	2.0 g	2.0 g
liquid paraffine	10.0 g	10.0 g	10.0 g
methyl p-hydroxybenzoate	0.1 g	0.1 g	0.1 g
18-beta-glycirretic acid	1.0 g	1.0 g	1.0 g
alpha-tocopheryl acetate	0.5 g	0.5 g	0.5 g
BHT	0.3 g	0.3 g	0.3 g

Aqueous phase			
glycolic acid	3.0 g	3.0 g	3.0 g
matè extract (caffeine 7%)	-	-	2.0 g
decaffeinated matè extract	2.0 g	2.0 g	-
ascobic acid (vitamin C)	0.01 g	0.01 g	0.01 g
deionized water q.b.	to 100 g	to 100 g	to 100 g

As it can be noted, the topical formulations contain no CLA, CLA alone, and CLA with caffeine, respectively.

Applicative Exemple 3 – Clinical trial of anticellulite activity by topical application of CLA and CLA with a xantine

9 female subjects were selected based on their cellulite intensity in the thigh area having a bi-lateral symmetry. Subjects with grades 1 and 2 cellulite were chosen, as a 5-point grading scale was used to rate the cellulite severity of each subject. The scale ranged from 0 to 4, being 0 = No cellulite; 1 = Small bumps or depressions; 2 = Striations and bumps; 3 = Pronounced lumpiness of the skin and striations; 4 = All of the above plus hard sub-surface nodules.

The subjects were divided in 3 groups of 3 individuals each, and instructed to apply in the right thigh the compositions of Comparative Example 3, the one of Applicative Example 4, and the one of Applicative Example 5, respectively.

The subject were taught to carried out the application two times a day, at morning and at night, during 2 months. Afterwards the cellulite condition were evaluated according Smith WP (Cosmetics & Toiletries, 61-70, June 1995), by comparison of the right thigh versus left thigh. Results are

illustrated in Table 2.

TABLE 2

Change of the cellulite condition after 2 month application

Condition	Cream of Comparative Example 3	Cream of Applicative Example 4	Cream of Applicative Example 5
Thigh diameter	-1%	-5%	-8%
Fatty layer thickness	-3%	-18%	-24%
Subjective improvement	+10%	+33%	+50%
Clinical grading	+2%	+30%	+30%
Skin firmness	+5%	+10%	+15%
Irritation reactions	2	0	3
Skin hydration	+25%	+13%	+24%
Surface smoothness	+14%	+21%	+37%

The results above show that the composition containing CLA effectively ameliorate the cellulite condition, with a further improvement by the combination with caffeine.

Applicative Example 4 – Kit for the cellulite treatment

An oily mixture (a) and a hydroalcoholic solution (b) were separately prepared by blending the following ingredients:

a) Ingredient of the oily mix

CLA from the Preparative Example 1	1.50 g
soya sterols	0.25 g
butylene glycol	1.50 g

vitamin E acetate	0.20 g
vitamin A palmitate	0.20 g
alpha bisabolol	0.10 g
asiaticoside	0.15 g
ethyl alcohol 94°	5.00 g
almond oil	q.b. to 20.00 ml

a) Ingredient of the aqueous mix

tributyl citrate	0.15 g
caffeine	0.15 g
ginkgo biloba extract	0.50 g
green tea extract	0.10 g
theophylline	0.20 g
glycolic acid	3.00 g
escin	0.05 g
18-beta-glycirretic acid	0.03 g
disodium EDTA	0.02 g
ethyl alcohol 94°	2.00 g
demineralized water	q.b. to 20 ml (*)

(*) Due to the low pH value, preservatives are not needed.

The two compositions were separately bottled in 25 ml jars and combined in the same kit package, along with the instruction to firstly apply (b) and, after 10 minutes to apply (a).

It should be understood that the specific forms of the invention herein illustrated and described are intended to be representative only. Changes, including but not limited to those suggested in this specification, may be

made in the illustrated embodiments without departing from the clear teachings of the disclosure. Accordingly, reference should be made to the following appended claims in determining the full scope of the invention.

CLAIMS

1. Use of Conjugated Linoleic Acid or a derivative thereof (CLA) for the topical treatment and/or prophylaxis of fatty deposits and cellulite.
2. Use of a topical composition which comprises Conjugated Linoleic Acid or a derivative thereof (CLA) for the treatment and/or prophylaxis of fatty deposits and cellulite.
3. Use according to claim 2, wherein the topical composition comprises from 0.5 to 70% by weight of CLA.
4. Use according to claims 2 or 3, wherein CLA derivatives comprise one or more cis and trans isomers of the 9,11- 10,12- and 11,13-octadecadienoic acids, its phospholipid and its mono-, di- and tri-glycerides, ethers, esters or salts thereof.
5. Use according to claim 4, wherein CLA salts are metallic soaps of alkaline and earthy-alkaline ions and the nitrogen-containing salts.
6. A cosmetic or dermatological topical composition which comprises Conjugated Linoleic Acid or a derivative thereof (CLA) in the form of a cream, gel, lotion, oil or spray, further comprising one or more further common anti-cellulite agents.
7. Cosmetic or dermatological topical composition according to claim 6, wherein said common anti-cellulite agent is a xanthine.
8. Cosmetic or dermatological topical composition according to claim 7, wherein said common anti-cellulite agent is selected among caffeine, theophylline, theobromine, aminophylline and mixture thereof.
9. A cosmetic or dermatological topical composition, which comprises Conjugated Linoleic Acid or a derivative thereof (CLA) for the treatment and/or prophylaxis of fatty deposits and cellulite, which further comprises a vanadium compound.
10. Method of treatment and/or prophylaxis of fatty deposits and cellulite which comprises topically administering Conjugated Linoleic Acid or a derivative thereof (CLA) or a composition according to claims 6 to 9.

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(71) Applicant and
(72) Inventor: GHISALBERTI, Carlo [BR/BR]; Rua Luis Dias, 85/61, Itaim-Bibi, CEP-04542-080 São Paulo, SP (BR).

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(54) Title: USE OF CONJUGATED LINOLEIC ACID (CLA) FOR THE TOPICAL TREATMENT OF CELLULITE

(57) Abstract: The present invention relates to the use of conjugated linoleic acid (CLA) for the topical treatment of fatty deposits and cellulite and to new topical compositions and to cosmetic and dermatological topical compositions for the treatment of fatty deposits and cellulite comprising CLA as well as kits comprising CLA for said treatment.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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AND EXCLUSION OF INVENTOR(S) UNDER 37 C.F.R. 3.71

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

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Williams (Reg. No. 31066), Ann L. Gisolfi (Reg. No. 31956), Todd A. Wagner (Reg. No. 35399), Scott B. Familant (Reg. No. 35514), Kelly D. Talcott (Reg. No. 39582), Francis D. Cerrito (Reg. No. 38100), Anthony M. Insogna (Reg. No. 35203), Brian M. Rothery (Reg. No. 35340), Brian D. Siff (Reg. No. 35679), Michael J. Lyons (Reg. No. 37386), Garland T. Stephens (Reg. No. 37242), William J. Sipio (Reg. No. 34514), Nikolaos C. George (Reg. No. 39201), Stephen S. Rabinowitz (Reg. No. 40286), Ognjan V. Shentov (Reg. No. 38051), and Kenneth L. Stein (Reg. No. 38704), all of Pennie & Edmonds LLP, whose addresses are 1155 Avenue of the Americas, New York, New York 10036, 1667 K Street N.W., Washington, DC 20006 and 3300 Hillview Avenue, Palo Alto, CA 94304, all of Pennie & Edmonds LLP (PTO Customer No. 20583), as its attorneys to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith, said appointment to be to the exclusion of the inventors and their attorney(s) in accordance with the provisions of 37 C.F.R. 3.71, provided that, if any one of these attorneys ceases being affiliated with the law firm of Pennie & Edmonds LLP as partner, counsel, or employee, then the appointment of that attorney and all powers derived therefrom shall terminate on the date such attorney ceases being so affiliated.

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ASSIGNEE: PENTAPHARM AG

Signature: i.V.

Typed Name: Caspar Stürm Olivier Kapp

Position/Title: CEO Manager, Legal Department

Address: Engelgasse 109, CH-4052, Basel, Switzerland

Date: March 27, 2002

DECLARATION FOR NON-PROVISIONAL PATENT APPLICATION*

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below at 201 et seq. beneath my name.

I believe I am the original, first and sole inventor if only one name is listed at 201 below, or an original, first and joint inventor if plural names are listed at 201 et seq. below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

USE OF CONJUGATED LINOLEIC ACID (CLA) FOR THE TOPICAL TREATMENT OF CELLULITE

and for which a patent application:
□ is attached hereto and includes amendment(s) filed on *(if applicable)*
□ was filed in the United States on as Application No. *(for declaration not accompanying application)*
with amendment(s) filed on *(if applicable)*
☒ was filed as PCT international Application No. PCT/IB00/01280 on September 8, 2000 and was amended under PCT Article 34 on November 28, 2001. *(if applicable)*

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED PRIOR TO THE FILING DATE OF THE APPLICATION			
APPLICATION NUMBER	COUNTRY	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
MI99A001894	Italy	September 9, 1999	YES ☒ NO □
			YES □ NO □
			YES □ NO □

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PROVISIONAL APPLICATION NUMBER	FILING DATE

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

201	FULL NAME OF INVENTOR	LAST NAME GHISALBERTI	FIRST NAME Carlo	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY São Paulo, SP BRX	STATE OR FOREIGN COUNTRY Brazil	COUNTRY OF CITIZENSHIP Brazil
	POST OFFICE ADDRESS	STREET Rua Luis Dias, 85/61, Itaim-Bibi, CEP-04542-080	CITY São Paulo, SP	STATE OR COUNTRY Brazil / ZIP CODE
		SIGNATURE OF INVENTOR 201 Carlo Ghisalberti		DATE 25 MARCH 2002
202	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE OR COUNTRY / ZIP CODE
		SIGNATURE OF INVENTOR 202		DATE
203	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE OR COUNTRY / ZIP CODE
		SIGNATURE OF INVENTOR 203		DATE
204	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE OR COUNTRY / ZIP CODE
		SIGNATURE OF INVENTOR 204		DATE
205	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
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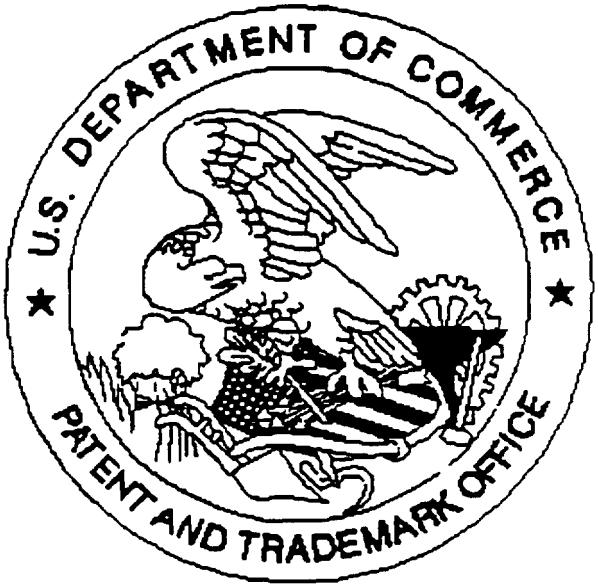

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